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L3: Entry 4 of 9 File: JPAB Aug 4, 1988

PUB-NO: JP363188623A
DOCUMENT-IDENTIFIER: JP 63188623 A
TITLE: UBIDECARENONE PREPARATION HAVING IMPROVED ABSORPTION

PUBN-DATE: August 4, 1988

INVENTOR-INFORMATION:
NAME COUNTRY
OZAWA, YASUO
YAMADA, KENJI
AKIMOTO, MASAYUKI
TANAKA, YOSHITAKA

ASSIGNEE-INFORMATION:
NAME COUNTRY
TAISHO PHARMACEUT CO LTD

APPL-NO: JP62021378
APPL-DATE: January 31, 1987

INT-CL (IPC): A61K 31/12; A61K 31/12; A61K 47/00; C07C 50/28

ABSTRACT:

PURPOSE: To obtain a preparation for oral administration, by adding a middle- chain fatty acid monoglycerin ester to ubidecarenone.

CONSTITUTION: 1pt.wt. ubidecarenone is blended with 0.5∼150pts.wt. middle-chain fatty acid monoglycerin ester (e.g. capric acid, caproic acid, caprylic acid, etc.) to give a preparation for oral administration having high absorption of ubidecarenone. The middle-chain fatty acid monoglycerin ester may be mixed with a third component such as vegetable oil, etc., and used as a mixture. The blending ratio of the third component is preferably 0.2∼1pt.wt. based on 1pt.wt. of the ester.

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L6: Entry 12 of 13 File: DWPI Aug 4, 1988

DERWENT-ACC-NO: 1988-260484
DERWENT-WEEK: 198837

TITLE: Absorption-improved ubidecarenone prepn. - contg. ubidecarenone and middle chain fatty acid mono:glycerine ester(s), pref. e.g. capric acid

PATENT-ASSIGNEE:

ASSIGNEE	CODE
TAISHO PHARM CO LTD	TAIS

PRIORITY-DATA: 1987JP-0021378 (January 31, 1987)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP 63188623 A	August 4, 1988		003	

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
JP 63188623A	January 31, 1987	1987JP-0021378	

INT-CL (IPC): A61K 31/12; A61K 47/70; C07C 50/28

ABSTRACTED-PUB-NO: JP 63188623A
BASIC-ABSTRACT:

An oral prepn. contg. ubidecarenone and middle-chain fatty acid monoglycerine esters.

Specifically pref. proportion of middle-chain fatty acid monoglycerin ester and ubidecarenone is 0.5-150 pts. wt. and 1 pts. wt. respectively. Pref. middle-chain fatty acid is capric acid, caproic acid, caprylic acid, etc. Plant oils can be added as a third component. Pref. their proportion to middle-chain fatty acid monoglycerin ester (1 pts. wt.) is 0.2-1 pts. wt.

USE/ADVANTAGE - Ubidecarenone, also called Coenzyme Q10, is used for cardiac incompetence and improvement of cardiac functions. However, ubidecarenone is hardly sol. in water and absorption when administered orally is bad. In order to improve absorption, ubidecarenone soft capsule is developed, but its absorptivity is still insufficient. This invention presents a new ubidecarenone oral prepn. whose absorptivity is good.

CHOSEN-DRAWING: Dwg.0/0

TITLE-TERMS: ABSORB IMPROVE UBIDECARENONE PREPARATION CONTAIN UBIDECARENONE MIDDLE CHAIN FATTY ACID MONO GLYCEROL ESTER PREFER CAPRIC ACID

ADDL-INDEXING-TERMS:
COENZYME

DERWENT-CLASS: B05

CPI-CODES: B10-A06; B10-E04C; B12-F01B; B12-M11;

CHEMICAL-CODES:

Chemical Indexing M2 *01*
Fragmentation Code
G018 G100 H5 H542 H7 H723 H8 K0 L9 L951
M210 M211 M226 M232 M240 M272 M282 M320 M414 M431
M510 M520 M531 M540 M782 M903 M904 P522 V0 V801
Specfic Compounds
03245M
Registry Numbers
3102R 1678D

Chemical Indexing M2 *02*
Fragmentation Code
H4 H402 H482 H8 J0 J011 J2 J271 M210 M216
M220 M221 M222 M223 M224 M225 M231 M262 M281 M313
M321 M332 M343 M383 M391 M416 M431 M620 M782 M903
M904
Markush Compounds
198837-14901-M
Registry Numbers
3102R 1678D

Chemical Indexing M6 *03*
Fragmentation Code
M903 P522 R031 R111 R280 R301
Registry Numbers
3102R 1678D

SECONDARY-ACC-NO:
CPI Secondary Accession Numbers: C1988-116001

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L6: Entry 8 of 13 File: JPAB Aug 4, 1988

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DOCUMENT-IDENTIFIER: JP 63188623 A
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⑲日本国特許庁(JP)　⑪特許出願公開

⑫公開特許公報(A)　昭63－188623

⑤Int.Cl.⁴	識別記号	庁内整理番号
A 61 K 31/12	ABN ACX	7330－4C
47/00 // C 07 C 50/28	314	E－6742－4C

⑬公開　昭和63年(1988)8月4日

審査請求 未請求　発明の数 1　(全3頁)

⑭発明の名称　吸収改善ユビデカレノン製剤

⑳特　願　昭62－21378

㉒出　願　昭62(1987)1月31日

㉗発明者　小沢　康雄　東京都豊島区高田3丁目24番1号　大正製薬株式会社内

㉗発明者　山田　憲司　東京都豊島区高田3丁目24番1号　大正製薬株式会社内

㉗発明者　秋元　雅之　東京都豊島区高田3丁目24番1号　大正製薬株式会社内

㉗発明者　田中　善孝　東京都豊島区高田3丁目24番1号　大正製薬株式会社内

㉑出願人　大正製薬株式会社　東京都豊島区高田3丁目24番1号

㉔代理人　弁理士　北川　富造

明　細　書

1．発明の名称

吸収改善ユビデカレノン製剤

2．特許請求の範囲

ユビデカレノンに中鎖脂肪酸モノグリセリンエステル類を添加すること特徴とする経口投与製剤。

3．発明の詳細な説明

[産業上の利用分野]

本発明は経口吸収性に優れたユビデカレノン製剤に関する。

[従来の技術]

ユビデカレノンはコエンザイムQ₁₀またはユビキノン10とも呼ばれるキノリン誘導体であり、心不全患者の循環動態の改善、心機能低下の予防および鬱血性心不全に伴う呼吸困難、浮腫などの改善に有効な医薬として広く使用されている。しかし、この化合物は水に極めて溶け難く、従ってこれを経口投与したときの吸収性に難点があった。そのため、特に固形製剤などでは内服した場合、消化液中への分散が悪く、吸収性に悪影響を及ぼしていた。

こうした問題点を解決する目的でユビデカレノンを油脂類に溶解または分散させた軟カプセル剤が開発、市販されている。

[発明が解決しようとする問題点]

しかしながら、この様な市販の軟カプセル剤も吸収性において満足し得るものではなく、さらに吸収性に優れた製剤の開発が望まれている。

[問題点を解決するための手段]

本発明者らは前記問題点に鑑み、ユビデカレノン含有製剤の経口吸収性を高めるべく、鋭意検討した結果、ユビデカレノンに中鎖脂肪酸モノグリセリンエステル類を添加した経口投与製剤が上記

目的を達成することを見出し、本発明を完成した。

本発明において、中鎖脂肪酸モノグリセリンエステル類のユビデカレノンに対する添加割合は特に限定されないが、通常ユビデカレノン1重量部に対して中鎖脂肪酸モノグリセリンエステル類0.5～150重量部である。

中鎖脂肪酸モノグリセリンエステル類の中鎖脂肪酸として好ましいものとしてはカプリン酸、カプロン酸およびカプリル酸などである。

また、上記中鎖脂肪酸モノグリセリンエステル類に植物油などの第三成分を添加して混合物としても良い。この割合も特に限定されないが、通常中鎖脂肪酸モノグリセリンエステル類1重量部に対して、第三成分は0.2～1重量部であることが好ましい。

[発明の効果]

本発明によりユビデカレノンの吸収性を高めた経口投与製剤を提供することができる。

[実施例]

以下、実施例および試験例を挙げて本発明を具体的に説明する。

実施例1

ユビデカレノン1gをカプリン酸モノグリセリンエステル149gに加温溶解して、ユビデカレノン0.67%溶液を調製した。

実施例2

ユビデカレノン1gをカプリン酸モノグリセリンエステル：大豆油＝1：1の混合液149gに加温溶解して、ユビデカレノン0.67%溶液を調製した。

実施例3

ユビデカレノン1重量部をカプリン酸モノグリセリンエステル9重量部に加温溶解し、常法により軟カプセル剤を調製した。

実施例4

カプリン酸モノグリセリンエステル30重量部にユビデカレノン1重量部を加え、加温溶解して、常法により0号カプセルに充填した。

実施例5

ユビデカレノン10重量部とカプリン酸モノグリセリンエステル10重量部を混和、加温溶解し、この溶液をヒドロキシプロピルセルロース20重量部、結晶セルロース30重量部および乳糖29重量部の混合物に均一に分散させた。

次いで、この分散物を乾燥整粒後、ステアリン酸マグネシウム1重量部を混合し、1錠100mgの錠剤を圧縮成形した。

試験例1

(試験動物)

試験実施前日より絶食させたビーグル犬(体重10～13kg)を1群3頭用いた。

(検体)

以下のカプセル剤を検体とした。

検体1：実施例1の組成物を硬カプセル剤に充填したもの(1カプセル中ユビデカレノン10mg含有)。

検体2：市販軟カプセル剤(1カプセル中ユビデカレノン10mg含有。基剤としてプロピレングリコールジカプリン酸を使用していた。)

(投与方法)

ビーグル犬に各検体(ユビデカレノン20mg/㎏)を経口投与し直後に水30mlを強制的に投与した。

(試験方法)

血液試料の採取と処理

検体投与直前、投与後1時間、2時間、3時間、4時間、5時間、7時間および24時間ごとに前腕静脈より血液5mlを採取し、遠心分離後の血漿を試料とした。

定量法

各血漿中のユビデカレノン濃度は高速液体クロマトグラフィー法により測定した。[小沢ら、アルツナイミッテル フォルシュング(Arzneim-Forsch)第36巻、第689頁、1986年]すなはち、血漿0.5mlに蒸留水0.5mlを加え、エタノール・ヘキサン混液(2：5)7mlで抽出した。次にヘキサン層4mlを蒸発乾固し、残渣に希硫酸0.5mlと2%塩化第二鉄0.5mlを

添加した。その後５０℃、３０分間インキュベートした後、ｎ－ヘキサンを５ｍｌ加えて再抽出し、蒸発乾固した残渣にアセトニトリルを加えてから、このものを高速液体クロマトグラフに注入した。　カラムは、長さ１５０㎜、直径４㎜のものを用い、充填剤としてはＴＳＫ－Ｇｅｌ　ＬＳ－４１０（東洋ソーダ製）を用いた。溶離液はメタノール－エタノール－アセトニトリル－水（４８：４８：２：２）の混液を用いた。検出は２７３ｎｍのＵＶ吸収を使用した。

（試験結果）

検体投与直前の血漿濃度をさしひいた各採血時点の平均濃度を表１に示した。

本発明の製剤は対照検体よりも優れた経口吸収を示した。

表１　　各検体投与後の血漿

検体	ユビデカレノンの血漿中濃度；単位μg／ml						
	１時間後	２時間後	３時間後	４時間後	５時間後	７時間後	２４時間後
1	0.04 (±0.01)	0.33 (±0.02)	0.30 (±0.02)	0.43 (±0.07)	0.44 (±0.09)	0.44 (±0.08)	0.22 (±0.09)
2	0.05 (±0.01)	0.15 (±0.03)	0.15 (±0.03)	0.13 (±0.04)	0.07 (±0.02)	0.15 (±0.06)	0.05 (±0.02)

（　）内は標準偏差

PTO: 2003-2536

Japanese Published Unexamined Patent Application (A) No. 63-188623, published August 4, 1988; Application Filing No. 62-21378, filed January 31, 1987; Inventor(s): Yasuo Ozawa et al.; Assignee: 62-21378; Japanese Title: Absorption-Improved Ubidecarenone Tablets

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ABSORPTION-IMPROVED UBIDECARENONE TABLETS

CLAIM(S)

Tablets for oral intake characterized in that a middle fatty acid monoglycerin ester group is added to ubidecarenone.

DETAILED DESCRIPTION OF THE INVENTION

(Field of Industrial Application)

The present invention pertains to ubidecarenone tablets.

(Prior Art)

Ubidecarenone is a quinoline derivative generally called coenzyme Q10 or ubiquinone 10, and is widely used to improve blood circulation of patients with heart disease and to improve a respiratory problem caused by a defective heart function. This compound is not easily dissolved in water, so its absorption was a problem when orally taken in. Therefore, when it is processed into solid tablets and orally taken in, the dispersion into a digesting fluid is poor and is not absorbed well.

To solve such a problem, there has been developed and marketed soft gel capsules wherein ubidecarenone is dissolved or dispersed in a fatty group.

(Problems of the Prior Art to Be Addressed)

Even with these market-sold soft gel capsules, they were not totally satisfactory in absorption, and it has been demanded to develop tablets having more excellent absorption.

(Means to Solve the Problems)

The examiners of the present invention, taking the aforementioned problems into consideration, studied assiduously how to improve the absorption of ubidecarenone-containing tablets to be orally taken in. As a result, orally taken in tablets containing a middle chain fatty acid monoglycerine ester gourp in ubidecarenone can satisfy the aforementioned purpose and produced the present invention.

The ratio of the added middle chain fatty acid monoglycerine ester group relative to ubidecarenone is not specifically limited, but generally, to 1 part/weight of ubidecarenone, the middle fatty acid monoglycerine ester group is added by 0.5 – 150 parts/weight.

The preferred middle chain fatty acids out of a middle chain fatty acid monoglycerine ester group are caprylic acid, capric acid, and caproic acid.

It is also possible that a third component such as a vegetable oil is added to said middle chain fatty acid monoglycerine ester group to make an admixture. The mixing ratio in this case needs not be specified, but generally, the third component

is preferably 0.2 –1 part/weight relative to 1 part/weight of middle fatty acid monoglycerine ester group.

(Advantage)

The present invention can present tablets for oral intake that have improved absorption of ubidecarenone.

(Embodiment)

The present invention is explained below with reference to the embodiment example and test sample.

(Embodiment Example 1)

1 g of ubidecarenone was heated and dissolved in 149 g of monoglycerin caprate and a 0.67% ubidecarenone solution was thus prepared.

(Embodiment Example 2)

1 g of ubedecarenone was heated and dissolved in 149 g of admixture of monoglycerin caprate ester and soy beans oil with the mixing ratio 1 : 1 to prepare the ubidecarenone 0.67% solution.

(Embodiment Example 3)

1 part/weight of ubidecarenone was heated and dissolved in 9 parts/weight of monoglycerin caprate ester to prepared soft gel capsules by a conventional method.

(Embodiment Example 4)

1 part/weight of ubidecarenone was added to 30 parts/weight of monoglycerin caprate ester and heated and dissolved. This admixture was filled in No. 0 soft gel capsules by a conventional method.

(Embodiment Example 5)

10 parts/weigh of ubidecarenone and 10 parts/weight of monoglycerin caprate ester were mixed and dissolved by heat. This admixture solution was evenly dispersed in an admixture of hydroxypropyl cellulose 20 parts/weight, crystalline cellulose 30 parts/weight, and of lactose 29 parts/weight.

Subsequently, after this dispersed medium was dried and granulated, magnesium stearate was mixed by 1 part/weight. This mixture was compression-formed into tablets, each tablet having 100 mg.

(Testing on Animal)

3 beagle dogs (weight 10 – 13 kg) that were not fed were put into a group.

(Testing Sample)

The following capsule was used as a testing sample.

Testing sample 1: The one prepared by filling the composition of embodiment example 1 in hard capsules (1 capsule contained 10 mg of ubidecarenone.).

Testing sample 2: Market-purchased capsule (1 capsule contained 10 mg of ubidecarenone; propylene glycol dicaprate is used for the base.)

(Method of Intake)

Each testing sample was given to the Beagle dogs (ubidecarenone 20 mg/dog) by oral intake and water 30 ml was forcibly fed to the dogs.

(Testing Method)

Blood sample collection and treatment

Blood 5 ml was collected from the front arm vein every 1, 2, 3, 4, 5, 7, and 24 hours, respectively, and the blood plasma was prepared by putting them to centrifugal separation.

(Quantification Method)

The concentration of ubidecarenone in each plasma was measured by a high speed liquid chromatography method (Ozawa et el., Arzeim Forsch vol. 36, p 689, 1986). More specifically, distilled water 0.5 ml was added to 05 ml of plasma and extracted by using 7 ml of ethanol-hexane admixture (2 : 5). Then, the hexane layer 4 ml was put to evaporation and dried, and dilute sulfuric acid 0.5 ml and 2% ferrous chloride 0.5 ml were added to the residue. Subsequently, this admixture was incubated at 50°C for 30 minutes, and again extracted by adding n – hexane 5ml. After acetonitrile was added to the residue, this mixture was supplied to a high speed liquid chromatigraph column. The column was 150 mm long and its diameter was 4 mm. As to the filler, TSK-Gel LS-410 (Toyo Soda was used.) was used. For the eluting solution, methanol – ethanol – acetonitrile – water (48 : 48 : 2 :2) admixture was used. For detection, 273 nm UV absorption was used.

(Test Result)

Table 1 shows the average plasma concentration at a time of each blood collection from which the plasma concentration before the testing sample was given was subtracted. The tablets of the present invention demonstrated a better absorption rate for oral intake than that of reference (testing) samples.

Table 1 Plasma after each testing sample was given.

Testing sample	Concentration of ubidecarenone in the plasma: unit μg/ml						
	1 hour later	2 hours later	3 hours later	4 hours later	5 hours later	7 hours later	24 hours later
1	0.04 (+/1 0.01)	0.33 +/- 0.02	0.30 +/- 0.02	0.43 +/- 0.07	0.44 +/- 0.09	0.44 +/- 0.08	0.22 +/- 0.09
2	0.05 +/- 0.01	0.15 +/- 0.03	0.15 +/- 0.03	0.13 +/- 0.04	0.07 +/- 0.02	0.15 +/- 0.06	0.05 +/- 0.02

The value in ( ) indicates a standard deviation.

Translations
U. S. Patent and Trademark Office
3/25/03
Akiko Smith